UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,435	02/15/2002	M. Vijay Kumar	M0351-268908	3474

7590 10/13/2006

Cynthia B. Rothschild
Kilpatrick Stockton LLP
1001 West Fourth Street
Winston-Salem, NC 27101

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,435	KUMAR, M. VIJAY	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-12,16-22,25,26,28-38,42,43 and 45-52* is/are pending in the application.

4a) Of the above claim(s) *2-12, 16-22, 25-26,* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-38,42,43 and 45-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The finality of the previous Office action has been withdrawn, and the prosecution of this application is reopened to include art not previously cited.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 28-38, 42-43, 45-52 are being examined.

New Rejections Based on New Consideration

Claim Rejections - 35 USC § 112, First Paragraph, Scope

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-38, 42-43, 45-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising an effective amount of the TRAIL polypeptide comprising SEQ ID NO:1 and an antiprogestin, which effective amount increases the death receptor DR4 or DR5 in a portion of the treated prostate cancer cells, does not reasonably provide enablement for a composition comprising an effective amount of a TRAIL polypeptide comprising SEQ ID NO:1 and an antiprogestin, wherein an effective amount of TRAIL polypeptide SEQ ID NO:1 and an antiprogestin results in an increase in "at least one death receptor" or "at least" one of DR4 or DR5, in a portion of the treated prostate cancer cells. The specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following *Wands* factors have been considered when the 112, first paragraph, enablement rejection was made:

The breadth of the claims

The breadth of the claims is broad.The claim 45 encompasses a composition of an effective amount of TRAIL and antiprogestin, which effective amount increases **any** death receptors, which death receptors do not necessarily have to be the receptor for the ligand TRAIL.

The nature of the invention

The nature of the invention is complex.

The state of the prior art

The prior art does not teach a composition of an effective amount of TRAIL and antiprogestin, which effective amount increases **any** death receptors. The prior art only teaches that the receptor for TRAIL ligand is DR4 and DR5 (see Bonavida et al in 103 rejection below).

The level of one of skill in the art

Although the level of skill in the field of molecular pathology is high, it would be undue experimentation for one of skill in the art to practice the claimed invention.

The level of predictability of the art

The level of unpredictability in the art is high.

On cannot predict that the TRAIL polypeptide and antiprosgestin would increase at least **any** one death receptor, for example, the death receptor FAS-R taught by Johnston (US 20060083738), because one cannot predict that TRAIL polypeptide would fit into any death receptor other than their own receptors, such as DR4 or DR5, in view that although there is certain plasticity in ligand-receptor interactions, the ligand has to have a certain binding stability, and has to have molecular configuration specificity, for example, a certain configuration for perfect fit into the receptor for activation of the receptor, like lock and key.

Working example and The amount of direction provided by the inventor

The specification only discloses that in PC3 androgen insensitive and androgen responsive prostate cancer cells, the DR4 and DR5 levels increase after treatment with TRAIL (p.31, second paragraph). The specification does not have any objective evidence that treatment with TRAIL and an anti-progestin or Mifepristone increases the level of any cell death receptor.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification.

In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 28-38, 45-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonavida, B et al, 1999 (Intl J Oncology, 15(4): 793-802, of record), in view of Wiley et al (WO 97/01633-A1), El Etreby et al, 2000 (The Prostate 42: 99-106, IDS # 27, submitted on 11/12/02, of record), and El ETreby et al, 1998 (Breast Cancer Res Treat, 51: 149-168).

Claims 28-30 are drawn to: A composition for treating prostate cancer by inducing cell death in androgen responsive and androgen independent prostate cancer cells comprising an effective amount of **a Tumor necrosis factor alpha - Related Apoptosis Inducing Ligand (TRAIL)** (emphasis added) polypeptide comprising the amino acid sequence SEQ ID NO: 1 **and an antiprogestin, or Mifepristone** (emphasis added), in a pharmaceutical carrier, wherein an effective amount comprises sufficient TRAIL polypeptide and antiprogestin, or Mifepristone, to induce apoptosis in at least a portion of androgen responsive and androgen independent prostate cancer cells exposed to the composition such that the combination of the TRAIL and the antiprogestin, or Mifepristone, induces apoptosis in a greater number of the treated prostate cancer cells than the additive effect of TRAIL and the antiprogestin separately applied to the cancer cells.

Claims 31-32 are drawn to: The composition of claim 30, wherein the Mifepristone and the TRAIL polypeptide are packaged in such a manner that the-Mifepristone is at least partially released for application to the cancer prior to, or substantially simultaneously with the release of the TRAIL polypeptide.

Claims 33-35 are drawn to: The composition of claim 30, wherein the dose of TRAIL polypeptide results in a local concentration of TRAIL polypeptide at the prostate cancer which ranges from 1 to 1,000 ng/ml, or 200 to 600 ng/ml, or 350 to 450 ng/ml.

Claims 36-38 are drawn to: The composition of claim 30, wherein the dose of Mifepristone results in a local concentration of Mifepristone at the prostate cancer which ranges from 1 to 1,000 uM, or 1 to 100 uM, or 5 to 20 uM.

Claims 45-46 are drawn to: The composition of claim 28, wherein an effective amount of the TRAIL polypeptide and antiprogestin results in an increase in at least one death receptor in at least a portion of the treated prostate cancer cells (claim 45), wherein the death receptor is at least one of DR4 or DR5 (claim 46).

Claims 47-48 are drawn to: The composition of claim 28, wherein an effective amount of the TRAIL polypeptide and antiprogestin results in an increase in an activated caspase enzyme in at least a portion of the treated prostate cancer cells (claim 47), wherein the activated caspase enzyme comprises at least one of caspase-8, caspase-7, caspase-9, or caspase-3 (claim 48).

Claim 49 is drawn to: The composition of claim 28, wherein an effective amount of the TRAIL polypeptide and antiprogestin results in an increase in truncated BID protein (tBid) in at least a portion of the treated prostate cancer cells.

Claim 50 is drawn to: The composition of claim 28, wherein an effective amount of the TRAIL polypeptide and antiprogestin results in a reduction of mitochondrial cytochrome c in at least a portion of the treated prostate cancer cells.

Claim 51 is drawn to: The composition of claim 28, wherein an effective amount of the TRAIL polypeptide and antiprogestin results in an increase in apoptosome formation in at least a portion of the treated prostate cancer cells.

Claim 52 is drawn to: The composition of claim 28, wherein the antiprogestin and the TRAIL polypeptide are packaged in such a manner that the antiprogestin is at least partially released for application to the cancer prior to the release of the TRAIL polypeptide.

Bonavida, B et al teach a **combination of TRAIL and actinomycin D** for treating several tumor cells, including prostate cancer. Bonavida, B et al teach that several tumor cells, including prostate cancer, develop resistance to treatment with TRAIL, and a combination therapy of TRAIL with chemotherapeutic drugs could reverse the resistance to TRAIL (p.797, first column), such as treatment with actinomycin D overcomes resistance of Kaposi's sarcoma, and prostate cancer cell lines to TRAILs (p.798). Bonavida teach that two strategies can be used to sensitize resistant cancer cells to TRAIL-mediated apoptosis, one is the **suppression of** anti-apoptotic molecule, another is the up-regulation of pro-apoptotic molecule; for example **Bcl-XL and BCL-2, major inhibitors of the mitochondrial apoptotic pathway**, can be regulated by drugs (p.800, first column, item 7, Mechanism of TRAIL-resistance and sensitization). Bonavida teaches that conventional chemotherapy does not simply prevent cell replication, but in many cases induces a process of programmed cell death (p.800, second column, lines 2-4), and that for example, **Actinomycin D**, a drug that inhibits RNA synthesis, also **decreases the expression of Bcl-XL** (a death inhibitor or anti-apoptotic protein) (p.800, first column, item 7, Mechanism of TRAIL-resistance and sensitization). Bonavida, B et al teach that TRAIL apoptosis involves crossing of TRAIL receptors DR4, DR5 with the ligand TRAIL (p.794, second column, last paragraph).

It is noted that Bonavida's TRAIL polypeptide is SEQ ID NO:1, as evidenced by WO 97/01633-A1, which teaches a TRAIL polypeptide for treating cancer. The TRAIL polypeptide

taught by WO 97/01633-A1 is 100% similar to the TRAIL polypeptide SEQ ID NO:1 of the claimed invention, as shown in MPSRCH sequence similarity search (MPSRCH search report, 2005, us-10-077-435-1.rag, pages 2-3).

Bonavida, B et al do not teach an antiprogestin or Mifepristone in a combination with TRAIL. Bonavida, B et al do not teach: 1) packaging of Mifepristone and TRAIL, such that Mifepristone is at least partially released prior to the release of said TRAIL, or are released substantially simultaneously, 2) the dose of TRAIL, which ranges from 1 to 1,000 ng/ml, 200-600 ng/ml, 350-450 ng/ml, and 3) the dose of Mifepristone, which ranges from 1 to 1,000 uM, or 1 to 100 uM or 5 to 20 uM.

El Etreby et al, 2000, teach Mifepristone, an antiprogestin, which is a known inhibitor of mammary tumor, also significantly inhibit both androgen-sensitive (LNCaP) and androgen-insensitive (LNCaP-C4-2) human prostate cancer cells, grown in nude mice (see Results on pages 102-103). Fathy El Etreby et al teach that the antitumor action of antiprogestins is mediated via the progesterone receptor, and related to induction of apoptosis (p.100, first column, first paragraph).

El Eltreby et al, 1998, teach that treatment with Mifepristone **or** 4-hydroxy-tamoxifen induces 60% inhibition of Bcl2, a negative regulator of apoptosis, in a breast cancer cell line (p.150, first column, second paragraph, p.157, first column, item under Bcl2 protein expression, bridging second column, figure 2 on page 158).

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to substitute actinomycin D, in the composition of TRAIL and actinomycin D taught by Bonavida et al, with Mifepristone (an anti-progestin) taught by El Etreby et al,

1998, 2000, for use as a suppressor of the Bcl-anti-apoptotic protein together with TRAIL in the treatment of breast cancer, or androgen responsive or non-responsive prostate cancer, because of the following reasons:

Mifepristone is known to be a suppressor of an anti-apoptotic protein, Bcl2, which acts similarly to actinomycin D taught by Bonavida et al, which is a suppressor of the anti-apoptotic protein BclXL, as taught by El Eltreby et al, 1998.

Moreover, Bonavida et al also suggest that suppression of the Bcl anti-apoptotic molecules BclXL and Bcl2 is one of the two strategies to be used to sensitize those cancer cells that are resistant to TRAIL-mediated apoptosis.

In addition, it would have been obvious to package TRAIL and Mifepristone such that Mifepristone is partially released prior to the release of TRAIL or both are released simultaneously, because such mode of operation is common in the art when a combination of drugs are used, to increase the versitality of drug administration and the effectiveness of the drugs.

Moreover, it would have been obvious to treat cancers, using TRAIL concentrations, which range from 1 to 1,000 ng/ml, 200-600 ng/ml, 350-450 ng/ml, and Mifepristone concentrations, which ranges from 1 to 1,000 uM, or 1 to 100 uM or 5 to 20 uM, because to determine optimum concentration of reactants is within the level of ordinary skill in the art. See *In re Kronig*, 190 USPQ 425, and because "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

It is noted that although the combined art does not explicitly teach that: 1) a combination of TRAIL and anti-progestin or Mifepristone induces apoptosis in a greater number of the treated prostate cancer cells than the additive effect of TRAIL and the anti-progestin separately, 2) TRAIL and antiprogestin increase death receptor, which is DR4 or DR5, 3) TRAIL and antiprogestin increase an activated caspase, which is at least one of caspase-8, caspase-7, caspase-9 or caspase-3, 4) TRAIL and antiprogestin increase truncated BID, 5) TRAIL and antiprogestin reduce mitochondrial cytochrome C, or increase apoptosome formation, however, the claimed composition comprising TRAIL polypeptide and Mifepristone appears to be the same as the prior art suggested composition comprising TRAIL polypeptide and Mifepristone, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

2. Claims 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonavida, B et al, 1999 (Intl J Oncology, 15(4): 793-802, of record), in view of Wiley et al (WO 97/01633-A1), El Etreby et al, 2000 (The Prostate 42: 99-106, IDS # 27, submitted on 11/12/02, of record), and El Etreby et al, 1998 (Breast Cancer Res Treat, 51: 149-168), and further in view of Presta et al (20020146416, having as priority, March 18, 1994).

Claims 42-43 are drawn to: A kit for pharmaceutical treatment of androgen responsive and androgen independent prostate cancer comprising:

(a) a pharmacologically effective amount of a Tumor necrosis factor alpha - Related Apoptosis Inducing Ligand (TRAIL) polypeptide comprising the amino acid sequence SEQ ID NO: 1 packaged in a sterile container;

(b) a pharmacologically effective amount of an antiprogestin packaged in a sterile container~ wherein an effective amount comprises an amount of TRAIL polypeptide and antiprogestin sufficient to induce apoptosis in a greater number of androgen responsive and androgen independent prostate cancer cells than the additive effect of the TRAIL and the antiprogestin separately applied to the cancer cells;

(c) at least one aliquot of a pharmaceutical carrier; and

(d) instructions for application of the TRAIL polypeptide and the antiprogestin to a patient having prostate cancer such that application of both the TRAIL and the antiprogestin induces apoptosis at least a portion of the treated prostate cancer cells (claim 42), wherein the antiprogestin comprises Mifepristone (claim 43).

The teaching of Bonavida et al, WO 97/01633-A1, El Etreby et al, 2000, and El Etreby et al, 1998 has been set forth above.

Bonavida et al, WO 97/01633-A1, El Etreby et al, 2000, and El Etreby et al, 1998, do not teach a kit, nor a pharmaceutical carrier.

Presta et al teach that the therapeutic formulations of the present invention are prepared for storage by mixing the active ingredient having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical

Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions (para 0292). Presta et al teach that acceptable carriers, excipients or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN, Pluronics or PEG.

It would have been obvious to package TRAIL polypeptide and Mifepristone taught by Bonavida et al, WO 97/01633-A1, El Etreby et al, 2000, and El Etreby et al, 1998, in a kit and packaged in a sterile container, with instruction for use, for commercial application.

Moreover, it would have been obvious to formulate the TRAIL polypeptide and Mifepristone composition taught by Bonavida et al, WO 97/01633-A1, El Etreby et al, 2000, and El Etreby et al, 1998, in a pharmaceutical carrier, as taught by Presta et al, for storage of the polypeptides.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

MINH TAM DAVIS

September 25, 2006